Remarks

The claims have been amended in response to the Office Action. Claims 2-11, 14-20, 23-29, 34-50, 52-60, 65-72, and 77-84 have been cancelled. Claim 1 has been amended in response to the Office Action. Applicants assert that the amendment to claim 1 introduces no new matter as it embraces a subset of the originally claimed subject matter. Claims 12 and 21 have been amended to correct an obvious typographical error. Claim 13 has been amended to modify the definition of variables R^1, R^2, R^3, and X. Applicants assert that the amendment to Claim 13 presents no issue of new matter. Basis for these amendments may be found on page 6 of the specification at lines 12-16 and 18-19. Claim 22 has been amended to modify the definition of variables R^1, R^2, and R^3. Applicants assert that the amendment to Claim 22 presents no issue of new matter. Basis for these amendments may be found on page 6 of the specification at lines 13-16 and 18-19. Claims 85 and 86 have been amended to correct typographical errors and Claim 86 has been placed in dependent form. Basis for the amendment to claim 85 may be found in Examples 279 and 279(a) on pages 215 – 218 of the application. Basis for the amendment of claim 86 may be found in Examples 327(a) and 327(b) on pages 258 – 260 of the application. New claim 87 has been added to more precisely claim specific aspects of the invention, and is drawn to pharmaceutical compositions comprising the compound of Claim 85. Claims 1, 12-13, 21-22, 30-33, 51, 61-64, 73-76, and 85-87 are currently pending. Entry of the amendments and allowance of the claims in view of the amendments and following discussion are respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 7, 8, 12, 13, 21, 22, 27, 28 and 86 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter applicants regard as their invention. Each basis for this rejection will be addressed in the order presented by the Examiner in the following paragraphs.

a) Claim 7 has been cancelled, thereby obviating this rejection.

b) Claim 8 has been cancelled, thereby obviating this rejection.

c) Claim 8 has been cancelled, thereby obviating this rejection.

d) Claim 12 has been amended to correct an obvious typographical error, replacing variable "R2" with variable "R^2". Applicants assert that the representation "R^2" finds antecedent basis in Claim 1 and, therefore, the requirements of 35 U.S.C. § 112, second paragraph are fully met.

e) Claim 13 has been amended such that R^3 is now defined to be "(C_{1-4}) alkyl". Applicants assert that this definition for R^3 finds antecedent basis in Claim 1 and, therefore, the requirements of 35 U.S.C. § 112, second paragraph are fully met.

f) Claim 13 depends from claim 12. In view of the amendment to claim 12, Applicants assert that the representation "R^2" now finds antecedent basis in claim 12 and, therefore, the requirements of 35 U.S.C. § 112, second paragraph are fully met.

g) Claim 21 has been amended to correct an obvious typographical error, replacing variable "R2" with variable "R^2". Applicants assert that the representation "R^2" finds antecedent basis in Claim 1 and, therefore, the requirements of 35 U.S.C. § 112, second paragraph are fully met.

h) Claim 22 depends from claim 21. In view of the amendment to claim 21, Applicants assert that the representation "R^2" now finds antecedent basis in claim 21 and, therefore, the requirements of 35 U.S.C. § 112, second paragraph are fully met.

i) Claim 27 has been cancelled, thereby obviating this rejection.

j) Claim 28 has been cancelled, thereby obviating this rejection.

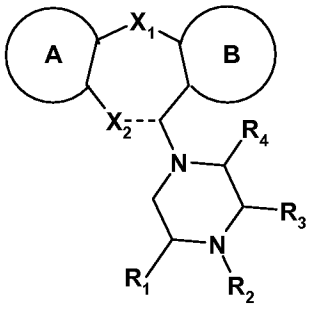
k) Claim 86 has been amended to reflect that the methoxy moiety is attached to an ethyl group rather than a methyl group.

Withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph in view of the amendments and preceding comments is respectfully requested.

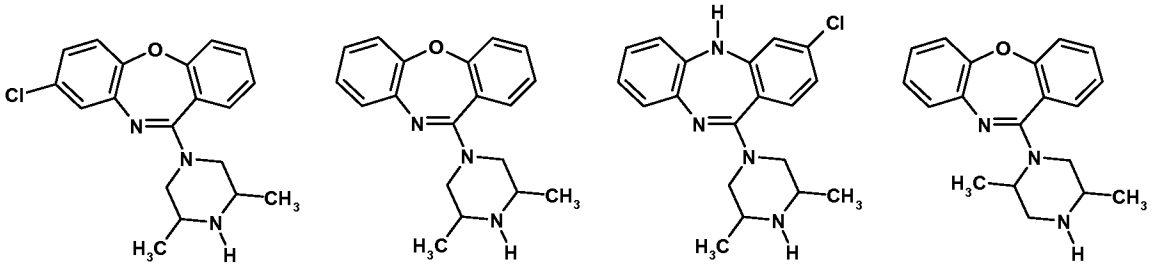
Rejections Under 35 U.S.C. § 103

Now pending claims 1, 12, 13, 21, 22, 30-33, 51, 61-64, 73-76, 85 and 86 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tehim *et al.*, U.S. Patent #5,824,676 (Tehim). The Examiner supports this rejection by arguing that the generic expression in Tehim (Formula I, column 1) encompasses the presently claimed compounds and the genus of compounds described by Tehim are also taught to be useful as antipsychotics. Specifically, the Examiner notes that the piperazine substituents generically taught in Tehim encompass the piperazine substituents allowed in compounds of the present invention. Applicants respectfully submit that the Examiner's conclusion in view of these facts is incorrect, and that Tehim would in no way motivate the skilled artisan to prepare the compounds of the present invention.

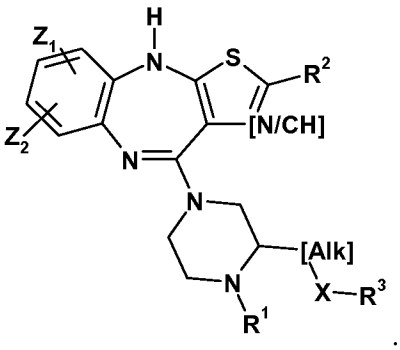
Tehim discloses the following genus of compounds:



wherein: A and B are independently selected, optionally substituted, saturated or unsaturated 5- or 6-membered homo- or heterocyclic rings; X_1 is CH_2, O, NH, S, C=O, CH-OH, CH-N(C_{1-4} alkyl)$_2$, C=CHCl, C=CHCN, N-(C_{1-4} alkyl), N-acetyl, SO_2, or SO; X_2 is N=, CH=, C(O)-, O-, or S-; R_1 is C_{1-6} alkyl optionally substituted with a substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} alkoxy; and R_2, R_3, and R_4 are independently selected from H and R_1. In contrast to the breadth of this generic expression, however, Tehim exemplifies only the following 4 compounds:



In all four of these compounds, rings A and B are both phenyl and the only non-hydrogen variable on the piperazine ring is methyl. The currently claimed compounds are of the following formula:



At issue is whether Tehim, considered as a whole, would motivate the skilled artisan to modify these prior art compounds by: a) replacing the phenyl ring corresponding to ring B in Tehim with either a thiophene or thiazole; and b) replacing one piperazine ring methyl group with hydrogen and the other with the variable –[Alk]-X-R^3 to provide the compounds of the present invention.

As a threshold matter, "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." (*In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) (citing *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)) Furthermore, "mere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious." (*Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 81 USPQ2d 1324, 1331 (Fed. Cir. 2006) (citing *In re Kahn*, 78 USPQ2d 1329 (Fed. Cir. 2006)). Finally, it is fundamental that the prior art must give the reason or motivation to make the claimed compounds to establish *prima facie* obviousness. (*In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)) Applicants strongly assert that Tehim provides no such reason or motivation to modify the prior art compounds to arrive at the compounds of the present invention.

With respect to the tricyclic ring system, Tehim defines rings A and B such that each is independently optionally substituted, saturated or unsaturated 5- or 6-membered homo- or heterocyclic rings. In addition to this very broad description, additional guidance is provided for "particular embodiments" where "ring A is benzene and ring B is selected from benzene, pyridine, triazole, pyrazole, thiophene, thiazole, furan and pyran; and is particularly selected from benzene and pyridine." (Tehim, column 3, lines 4-8) To the extent that a preference for a ring B heterocycle is stated, it is limited to pyridine although both A and B are phenyl in all of the exemplified compounds. As such, Tehim provides no motivation to modify the ring B phenyl of the exemplified compounds to arrive at the currently claimed thiophenes or thiazoles.

With respect to the piperazine carbon substituents, variables R_1, R_3, and R_4, Tehim exemplifies only compounds where R_1 is methyl and R_3 and R_4 are either hydrogen or methyl. Tehim generically defines R_1 to be C_{1-6} alkyl optionally substituted with a substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} alkoxy; and R_3, and R_4 are independently selected from H and R_1. "Particular embodiments" are taught to be those where R_1 is C_{1-6} alkyl, more particularly methyl or ethyl, and specifically methyl. (Tehim, column 2, lines 41-45). Additional "particular embodiments" are those where R_3 and R_4 are independently selected from H and methyl. (Tehim,

column 2, lines 46-54). This teaching, in combination with the exemplified compounds, leads the skilled artisan to compounds where the piperazine ring is substituted on its carbon atoms with one or two methyl groups. The compounds of the present invention, by contrast, bear a single piperazine carbon substituent selected from the complex variable –[Alk]-X-R^3, where Alk is (C_{1-4}) alkylene or hydroxy substituted (C_{1-4}) alkylene; X is oxygen or sulfur; R^3 is hydrogen, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, Ar, or (C_{1-4})alkyl-Ar; and Ar is optionally substituted phenyl, napthyl, monocyclic heteroaromatic or bicyclic heteroaromatic. The skilled artisan will appreciate that even small changes in the piperazine ring may give rise to dramatic changes in the pharmacology of the molecule. (**See:** Chakrabarti, *et al.*, *Journal of Medicinal Chemistry*, **25**(10), 1133, 1136 (1982); reference CA on 1449 form (last paragraph, third sentence)) Nothing in Tehim would motivate the skilled artisan to modify a methyl group of the prior art compounds to arrive at the more complex substituents of the present compounds. Furthermore, there could be no expectation of success given the art-recognized sensitivity of this type of molecule to structural changes in the basic region.

Conclusion

The claims have been amended to address issues raised by the Examiner. The presently claimed compounds differ from the prior art molecules identified by the Examiner in two distinct regions. The prior art relied-upon by the Examiner provides no motivation to make either of these modifications. Furthermore, the art teaches that one requisite modification, substitution in the piperazine ring, gives highly unpredictable results. As such, the Examiner's finding of *prima facie* obviousness is improper and should be withdrawn. Entry of the amendments and withdrawal of the rejections in view of the amendments and discussion are respectfully requested.

Respectfully submitted,

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